FABRICATION AND EVALUATION OF BUCCOADHESIVE TABLETS OF ESOMEPRAZOLE

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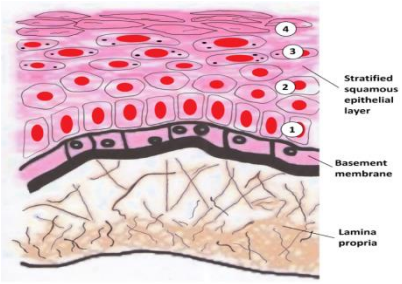
Abstract:

Esomeprazole is a proton pump inhibitor used to treat gastro esophageal reflux disease (GERD) and also used in combination with other medications for preventing stomach ulcers. The buccal mucosa is bordered vertically by the maxillary and mandibular vestibular folds, whereas its anterior and posterior borders are formed by the outer commissural of the lips and the anterior tonsillar pillar, respectively. Additionally there are limited sensory innervations from the facial nerve. The blood supply of the buccal mucosa originates primarily from. Amongst the various routes of drug delivery, oral routes perhaps the most preferred to the patient and the clinician alike. However, per oral administration of drugs has disadvantages such as hepatic first pass metabolism and enzymatic degradation within the GI tract, that prohibit oral administration of certain classes of drugs especially peptides and proteins. Consequently, these advantages include possible bypass of first pass effect, avoidance of presystemic elimination within the GI tract and depending on the particular drug, a better enzymatic flora for drug absorption. The buccoadhesive tablets of Esomeprazole. So, we made an attempt to prepare suitable buccoadhesive system for Esomeprazole to avoid acidic degradation of drug at stomach pH and also to avoid first pass hepatic metabolism. Among all, formulations F4 consists of Esomeprazole (20mg), carbopol (60mg), HPMC (20mg), microcrystalline cellulose (48mg), ethyl cellulose (50mg), magnesium stearate (2mg) was selected as best formulation. Various physiochemical parameters tested for this formulation showed good results. Good correlation was observed between *in-vitro* and *in-vivo* drug release profiles. Thus Esomeprazole is suitable candidate for oral controlled drug delivery via buccoadhesive tablets.

Key words: Buccal mucosa, Esomeprazole, Tonsillar pillar, enzymatic flora, controlled drug delivery.

Introduction:

Buccal mucosa composed of several layers of different cells .The epithelium is similar to stratified squamous epithelia found in rest of the body and is about 40–50 cell layers thick.Lining epithelium of buccal mucosa is the non keratinized stratified squamous epithelium that has thickness of approximately 500–600 μ and surface area of 50.2 cm^2. Basement membrane, lamina propria followed by the sub mucosa is present below the epithelial layer. Lamina propria is rich with blood vessels and capillaries that open to the internal jugular vein. Lipid analysis of buccal tissues shows the presence of phospholipid 76.3 %, glucosphingolipid 23.0 % and ceramide NS at 0.72 %. Other lipids include acyl glucosylated ceramide.The primary function of buccal epithelium is the protection of the underlying tissue. In non-keratinized regions, lipid-based permeability barriers in the outer epithelial layers protect the underlying tissues against fluid loss and entry of potentially harmful environmental agents such as antigens, carcinogens, microbial toxins and enzymes from foods and beverages·



Factors influencing drug absorption from the buccal cavity the two important factors, which influence oral transmucosal absorption of drugs are as follows. Absorption and onset of action whereas the buccal mucosa suits sustained delivery system. Permeability of the oral mucosa the lipoidal membranes of the oral mucosa are resistant to the passage of large macromolecules, but small-unionized molecules tend to cross the membrane relatively easily. The absorption of drug is found to be site-dependant due to differences in the epithelial thickness and extent of keratinization.Various mechanisms thought to be involved in drug absorption across the oral mucosa are passive diffusion, facilitated diffusion, active transport and pinocytosis.The sublingual mucosa is more permeable than the buccal mucosa. The sublingual mucosa is suitable for rapid absorption and onset of action whereas the buccal mucosa suits sustained delivery system. Physico-chemical characteristics of the drug are Molecular weight, Molecules penetrate the oral mucosa more rapidly than ions and smaller molecules more rapidly than larger molecules, and Degree of ionization, the average pH of saliva is 6.6. Because the unionized form of the drug possesses appreciable lipid solubility, both the pKa of the drug and the pH of the mucosa influence drug absorption. Absorption is maximum at a pH favoring the un-ionized form.Lipid solubility Partition co-efficient of 40-2000 is necessary for optimal drug absorption. If the partition co-efficient exceeds 2000, solubility in the saliva is insufficient to provide the concentration gradient necessary for drug absorption.Thus for satisfactory oral mucosal permeability, a drug should have low molecular weight, exhibit biphasic solubility pattern i.e. it should be soluble both in the aqueous saliva and the lipoidal membrane and a significant amount of the drug should be un-ionized at salivary pH. Also it should not be extensively or strongly bound to the oral mucosa. The Ideal Characteristics of Bucco Adhesive Polymers
Should have good spreadability, wetting, swelling, solubility and biodegradability properties. pH should be biocompatible and should possess good visco-elastic properties. Should adhere quickly to buccal mucosa and should possess sufficient mechanical strength. Polymer and its degradation products should be non-toxic, non-irritant and free from leachable impurities. Should demonstrate local enzyme inhibition and penetration enhancement properties. Should have optimum molecular weight and should possess peel, tensile and shear strengths at the bioadhesive range. Should have required spatial conformation.Should be sufficiently cross-linked but not to the degree of suppression of bond forming groups.Should not aid in development of secondary infections such as dental caries.

Material and methods:

Preparation of buccoadhesive tablets of esomeprazole

Buccaltablets containing Esomeprazole were prepared by direct compression method[56-59]. Various batches were preparedby changing the ratio of HPMC K 100, SCMC and Carbopol-934 to identify the most effective formulation

The drug and polymer mixture was prepared by homogeneously mixing the drug with HPMC K 100, SCMC, CP-934 (mucoadhesive polymers) and micro crystalline cellulose (binder)in a glass mortar for 15 minutes. Before direct compression, the powder were screened through a 60 µm sieve and thoroughly blended. The blend was lubricated with magnesium stearate for 3-5 min. The mixture (150 mg) was then compressed using an 8 mm diameter die in a 9-station rotary punching machine (Chamunda pharma pvt Ltd, Ahmedabad, India). The upper punch was raised and the backing layer of EC (50mg) was placed on the above compact. The two layers were then compressed into a mucoadhesive tablet. Each tablet weighed 200 mg and the composition of each formulation show on this table

Table No.1 Composition of BuccoadhesiveTablets of Esomeprazole

Formulation code		F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12
Ingredients (mg)	Esomeprazole	20	20	20	20	20	20	20	20	20	20	20	20
	HPMC K 100	80	-	-	20	40	60	-	-	-	20	40	60
	Carbopol 934	-	80	-	60	40	20	20	40	60	-	-	-
	SCMC	-	-	80	-	-	-	60	40	20	60	40	20
	MCC	48	48	48	48	48	48	48	48	48	48	48	48
	Mg. stearate	2	2	2	2	2	2	2	2	2	2	2	2

The present investigation was carried out by using following chemicals and instruments for buccal drug delivery of Esomeprazole tablets which are given in the Table No.2 and Table No.3

Table:2

S.No	Materials	Manufacturer
1	Esomeprazole magnesium	Giftsample from Reddy's lab, Hyderabad
2	Carbopol 934	Indian drugs, Hyderabad
3	Hydroxyl Propyl Methyl Cellulose	Indian drugs, Hyderabad
4	Sodium Carboxy Methyl Cellulose	Indian drugs, Hyderabad
5	Micro Crystalline Cellulose	Indian drugs, Hyderabad
6	Ethyl Cellulose	Indian drugs, Hyderabad
7	Magnesium stearate	Sd fine Chem.Ltd. Mumbai
8	Potassium di hydrogen phosphate	Sd fine Chem.Ltd. Mumbai
9	Di sodium hydrogen phosphate	Sd fine Chem.Ltd. Mumbai
10	Sodium hydroxide	Sd fine Chem.Ltd. Mumbai

Table:3

	Instruments	Manufacturer
1	Digital Balance	LCGC, Hyderabad
2	UV-Vis spectrophotometer	Shimadzu,India
3	FTIR Spectrophotometer	Shimadzu,India
4	Rotary Punching Machine	Chamunda pharma pvt Ltd, Ahmedabad
5	Monsanto Hardness tester	Singhala scientific industries, Ambala
6	Friabilator	Singhala scientific industries, Ambala
7	Dissolutiontestapparatus(USPTypeII)	Electro lab, Mumbai.(Model: TDT-08L)
8	Digital pH meter	Systronics, Hyderabad
9	Magnetic stirrer	Remi, Mumbai, India
10	Chein apparatus	Antian glass work, Madurai
11	Hot air oven	Biocraft scientific systems, Agra

Preformulation Studies

The preformulation studies are the first step in the development of any formulation. The major goal of this study is to establish compatibility of drug with that of the polymers used.In the present work, preformulation studies like

compatibility between drugs-polymers and flow properties were carried out. The results of preformulation studies were represented under chapter 6 (results and discussion).

Drug- Polymer Compatibility Studies

Drug polymer compatibility studies were performed by FTIR (Fourier Transform Infrared Spectroscopy) [60]. Infrared (IR) spectra were obtainedusing the KBr disk method (2 mg sample in 200 mg KBr). The scanning range was 400 to 4000 cm^{-1} and the resolution was 1 cm^{-1}. FTIR absorption spectra ofpure drugand all the polymers used like HPMC, SCMC, CP, MCC and EC the combination of drug and polymers shows no significant interaction between drug and polymers.

Flow Properties

Before formulation of drug substances into a dosage form, it is essential that drug polymer should be chemically and physically characterized. Preformulation studies gives the information needed to define the nature of the drug substance and provide a framework for the drug combination with pharmaceutical excipients in the manufacture of a dosage form.

Derived properties

Bulk Density

It was determined by pouring pre-sieved drug excipients blend into a graduated cylinder and measuring the volume and weight "as it is". It is generally expressed in g/mL and is given by,

$Db = M / V_O$ Where, M is the mass of powder and V_O is the Bulk volume of the powder.

Tapped density

It was determined by placing a graduated cylinder, containing a known mass of drug- excipients blend, on mechanical tapping apparatus. $D_T = M / V_T$Where, M is the mass of powder and V_T is the tapped volume of the powder.The tapped volume was measured by tapping the powder to constant volume. It is expressed in g/mL.

Powder flow properties

Angle of repose This is the maximum angle possible between the surface of the pile or powder and horizontal plane. Angle of repose was determined by using funnel method. The frictional forces in the lose powder can be measured by Angle of repose. The tangent of Angle of repose is equal to the coefficient friction between the particles. $\theta = \tan^{-1} (h / r)$ Where**,** θ is the angle of repose, h is the height in cm and r is the radius in cm.

Compressibility index

It is an important measure that can be obtained from the bulk andtapped densities. A material having values less than 20 to 30% is defined as the free flowing material. Based on the apparent bulk density and tappeddensity, the percentage compressibility of the bulk drug was determined by using the following formula. $I = D_T - D_b / D_T \times 100$ Where, I is the Compressibility index, Dt is the tapped density of the powder,D_b is the bulk density of the powder.

Hausner's ratio It indicates the flow properties of the powder and is measured by the ratio of tapped density to the bulk density $H = D_t / D_b$Where, H is the Hausner's ratio Dt is the tapped density of the powder and Db is the bulk density of the powder.

Table No.4 Limits for flow properties of powder

S.No	Type of flow	Angle of repose	Carr's index	Hausner's ratio
1	Excellent	25-30	10	1-1.11
2	Good	31-35	11-15	1.12-1.18
3	Fair	36-40(aid not needed)	16-20	1.19-1.25
4	Passable	41-45(may hang up)	21-25	1.26-1.34
5	Poor	46-55(must agitate)	26-31	1.35-1.45

6	Very poor	56-65	32-37	1.46-1.54
7	Very poor	>66	>38	>1.60

Results and discussions

Construction of calibration curve

The calibration curve of Esomeprazole was prepared by using phosphate buffer pH 6.8 and phosphate buffer pH 7.4 at 279 nm. The selection of two buffers (pH 6.8 and pH 7.4) is to mimic the buccal cavity pH and systemic pH respectively.

Preparation of 6.8 pH phosphate buffer(I.P 2010)

28g of disodium hydrogen phosphate and 11.45g of potassium dihydrogen phosphate in 1000ml volumetric flask and make up to 1000ml with distilled water.

Preparation of 7.4 pH phosphate buffer (I.P 2010)

50ml of 0.2M potassium dihydrogen phosphate solution was taken in 200ml volumetric flask. To this 39.1ml of 0.2M sodium hydroxide solution was added and finally the volume was made up to 200ml with distilled water.

Preparation of standard graph in phosphate buffer pH 6.8 and 7.4

100 mg of the drug (Esomeprazole) was dissolved in 6.8 pH Phosphate buffer and made up to 100 ml with the same to give a concentration of 1000 µg/ml. From this stock solution, 10 ml was taken and diluted to 100 ml with the same buffer to give the concentration of 100 µg/ml, from this 0.4, 0.8, 1.2…4ml of the solution was transferred to 10 ml volumetric flasks and made up to the volume with 6.8 phosphate buffer to give the concentrations of 4, 8, 12, ……40µg/ml, then the absorbance was measured at 279[55] nm against a blank using UV Spectrophotometer. Using these absorbance values the standard graph was plotted by taking concentration on X-axis and absorbance on Y-axis.

Same procedure was followed for the standard graph in phosphate buffer pH 7.4. The values were given in the Table No.5 and 6 respectively. And the graphs for both were given in Figure No.4 and 5.

Table No.5 Calibration curve data for Esomeprazole in phosphate buffer (pH 6.8)

Concentration (µg/ml)	Absorbance (279 nm)
4	0.11
8	0.223
12	0.314
16	0.447
20	0.507
24	0.593
28	0.697
32	0.799
36	0.874

40	0.989

Figure: Calibration Curve of Esomeprazole in Phosphate Buffer pH 6.

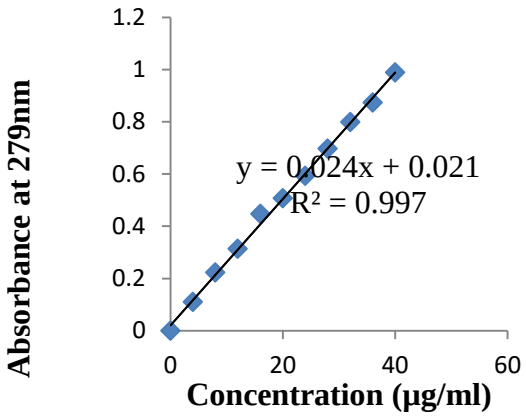
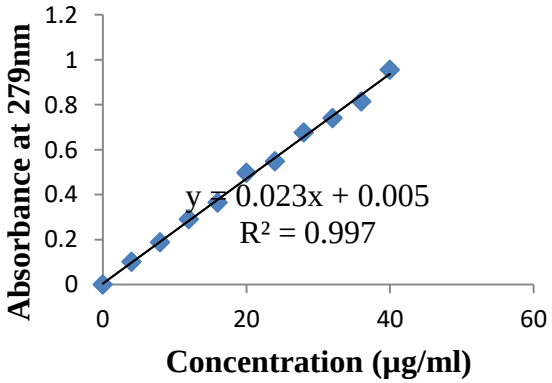


Table No: 6Calibration curve data for Esomeprazole in phosphate buffer (pH 7.4)

Concentration (µg/ml)	Absorbance (279 nm)
4	0.101
8	0.189
12	0.291
16	0.365
20	0.497
24	0.549
28	0.676
32	0.741
36	0.815
40	0.955

Figure : Calibration curve of Esomeprazole in phosphate buffer pH 7.4



Conclusion:

As per literature collected so far, no work has been done on buccoadhesive tablets of Esomeprazole. So, we made an attempt to prepare suitable buccoadhesive system for Esomeprazole to avoid acidic degradation of drug at stomach pHand also to avoid first pass hepatic metabolism. Esomeprazole buccoadhesive tablets were prepared by direct compression method using different buccoadhesive polymers such as Hydroxy Propyl Methyl Cellulose (HPMC), Sodium Carboxy Methyl Cellulose (SCMC) and Carbopol 934P along with Ethyl Cellulose (EC) as an impermeable backing layer.Drug-polymer compatibility studies by FTIR indicates there is no possible interactions between the drug and polymer and prepared tablets were characterized for their physico-chemical characteristics like thichness, hardness, friability, drug content, surface pH, swelling indexand results were within the limits of pharmacopoeia in all formulations(F1-F12). The *ex-vivo* buccoadhesive strength, *in-vitro* drug release, *ex-vivo* permeation and *in-vivo* drug release in rabbit shows reproducible results.Among all, formulations F4 consists of Esomeprazole (20mg), carbopol (60mg), HPMC (20mg), microcrystalline cellulose (48mg), ethyl cellulose (50mg), magnesium stearate (2mg) was selected as best formulation.Variousphysiochemical parameters tested for this formulation showed good results. Good correlation was observed between *in-vitro* and *in-vivo* drug release profiles. Thus Esomeprazole is suitable candidate for oral controlled drug delivery via buccoadhesive tablets. Further work is recommended to support its efficacy claims by long term pharmacokinetic and pharmacodynamic studies in human beings.

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